



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-D-6113]

E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials; International Council for Harmonisation; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled “E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.” The guidance was prepared under the auspices of the International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation. The guidance clarifies, updates, and extends the guidance for industry “E9 Statistical Principles for Clinical Trials” issued in September 1998 in two main areas. Concerning estimands, it provides a framework for discussion of how the aims of a trial relate to the proposed statistical analysis. Concerning sensitivity analysis, it discusses how to use additional analyses to address concerns about the validity of assumptions underlying the main analysis. The guidance is intended to better align the choice of statistical methods with questions of regulatory importance and so to improve the reliability of decisions about and representations of the effects of medical products. The guidance replaces the draft guidance issued on October 31, 2017.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2017-D-6113 for "E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at

<https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- **Confidential Submissions**--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002, or the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. The guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 240-402-8010. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: *Regarding the guidance:* Scott Goldie, Center for Drug Evaluation and Research, Food and Drug Administration, Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-796-2055, scott.goldie@fda.hhs.gov; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

Regarding the ICH: Jill Adleberg, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6364, Silver Spring, MD 20993-0002, 301-796-5259.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled “E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.” The guidance was prepared under the auspices of ICH. ICH has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, high-quality medicines are developed, registered, and maintained in the most resource-efficient manner.

By harmonizing the regulatory requirements in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies,

standardized the reporting of important safety information, standardized marketing application submissions, and made many other improvements in the quality of global drug development and manufacturing and the products available to patients.

The six Founding Members of the ICH are FDA; the Pharmaceutical Research and Manufacturers of America; the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; and the Japanese Pharmaceutical Manufacturers Association. The Standing Members of the ICH Association include Health Canada and Swissmedic. Additionally, the Membership of ICH has expanded to include other regulatory authorities and industry associations from around the world (refer to <https://www.ich.org/>).

ICH works by involving technical experts from both regulators and industry parties in detailed technical harmonization work and the application of a science-based approach to harmonization through a consensus-driven process that results in the development of ICH guidelines. The regulators around the world are committed to consistently adopting these consensus-based guidelines, realizing the benefits for patients and for industry.

As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance for industry. FDA's guidance documents do not establish legally enforceable responsibilities. Instead, they describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

In the *Federal Register* of October 31, 2017 (82 FR 50433), FDA published a notice announcing the availability of a draft guidance entitled "E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials." The notice gave interested persons an opportunity to submit comments by April 30, 2018.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Assembly and endorsed by the regulatory agencies in November 2019.

This guidance finalizes the draft guidance issued on October 31, 2017. The guidance provides clarification on statistical principles for clinical trials and an update on the choice of estimand to describe a framework for planning, conducting, and interpreting sensitivity analyses of clinical trial data. The focus of the guidance is on statistical principles related to estimands and sensitivity analysis for confirmatory clinical trials. The guidance provides recommendations for aligning the choice of statistical methods with the goals of a clinical trial; on communicating the rationale for such choices to FDA; and on using sensitivity analysis to characterize the robustness of the conclusions to plausible deviations from the assumptions of the main analysis. Revisions made following the public comment period are intended to clarify content within the guidance; however, no new concepts are presented in the revised version.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Electronic Access

Persons with access to the internet may obtain the guidance at <https://www.regulations.gov>, <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, or <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>.

Dated: May 7, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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